A Novel Approach to Conducting Dog Metabolism Studies allowing dogs to be pair housed – Enhancing Welfare and Science

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Background:
The understanding of Absorption, Distribution, Metabolism and Excretion (ADME) for new pharmaceuticals is required in regulatory submissions (1). Currently, ADME studies are conducted with metabolism cages involving single housing of animals for the collection of excreta. Even though such metabolism cages have limitations for animal welfare, they have been largely unchanged for 25-30 years. The improvement of animal welfare is a focus area at both Novo Nordisk and Covance. Therefore, a metabolism cage for dual housing was designed, in joint collaboration, to enhance welfare for dogs. In addition to Novo Nordisk and Covance ambitions, an increased focus on animal welfare has been defined in guidelines and legislation from the EU Commission (2, 3).

Description of initiative:
The purpose of this refinement initiative is to present data from dual and single housing of dogs (RCC Beagles, Envigo UK) in metabolism cages, to demonstrate the suitability of conducting excretion balance studies with a new pair housing design to improve welfare without compromising the scientific integrity of the study (overall recovery in excreta from dosed radioactivity). Additional refinement of welfare was introduced, including raised resting platform (solid) and perspex windows to improve interaction to the surrounding (animal to animal, animal to human).

Results:
The excretion balance evaluation has been conducted in metabolism cages with single and dual housed dogs, using the radiolabelled test compound, 14C Quetiapine an anti-psychotic pharmaceutical selected for its suitable excretion profile (including both urine and faecal elimination). Concentrations of radioactivity in blood and plasma were determined by liquid scintillation counting. Cortisol concentrations were also determined in serum samples daily. Urine and faeces were collected pre- and post-dose daily for up to 168 hours and the radioactivity was quantified. The overall mean recovery for pair housed animals, 94.0 ± 0.66% of the dose, was similar to that from single housed dogs, 93.0 ± 2.29%, and therefore considered equivalent. The faecal and urine excretion corresponded to in the ranges 72-77% and 13-20%, respectively, for both groups. The mean serum cortisol was higher for pair housed dogs at 0.5 hours and lower from 48 hours onwards. However, differences in serum cortisol should be treated with caution due to a large variation in cortisol levels.

Conclusion:
A new enriched metabolism cage for pair housing of dogs has been developed and demonstrated fit for the scientific purpose - and a major enhancement of animal welfare has been achieved.

Perspectives:
The impact of this initiative will affect approx. 16 dog per year estimated for NN and approx. 200 dog per year estimated for our collaborator Covance. It is too early for assessment of the dogs affected outside NN and Covance. However, this new concept will hopefully be a game changer for authorities, license holders and 3R decision makers moving towards the best possible alternative to traditional metabolism cages (with single housing of dogs). We hope that the good results from this study will be an inspiration for researchers to develop metabolism cages for group housing also in other species.

References:
1. ICH M3 (R2), Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceutical
2. Appendix A of Convention ETS 123. For the protection of vertebrate animals used for experimental and other scientific purposes